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09/581,345	09/27/2000	Ira H. Pastan	15280-339PC	2468

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/581,345	Applicant(s) PASTAN ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-112* is/are pending in the application.

4a) Of the above claim(s) *33-96* is/are withdrawn from consideration.

5)☒ Claim(s) *15-17* is/are allowed.

6)☒ Claim(s) *1,3-7,9-14,18-20,22-25,27-32,97-100,102-105 and 107-112* is/are rejected.

7)☒ Claim(s) *2,8,21,26,101 and 106* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-32 and 97-98, in Paper No. 12 is acknowledged. The traversal is on the ground(s) that "Applicants traverse the restriction and maintain that all the claims should be examined by the Examiner". This is not persuasive. Applicant has provided no evidence to establish why the requirement for restriction is improper. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**. EW 5/1/02

2. Claims 33-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

3. Claims 99-112 have been added. Claims 97 and 98 have been amended.

Claims 1-32 and 97-112 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate the instant application is claiming benefit to provisional application 60/067,175.

b. Page 8, line 14 and 25 should be updated to indicate the U.S. applications are now U.S. Patents and indicate the patent numbers.

Appropriate correction is required.

Claim R jecti ns - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 18, 19, 32, 98 108, and 109-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 18 recites the limitation "said animal" in lines 6-7. There is insufficient antecedent basis for this limitation in the claim. Claim 19 does not correct the deficiency.

b. Claim 32 is indefinite for reciting "said immunoconjugate is encoded by SEQ ID NO:2" because the exact meaning of the phrase is not clear. SEQ ID NO:2 is not an immunotoxin. SEQ ID NO:2 encodes for domains I and II of Pseudomonas exotoxin A (see page 43, line 21) and does not contain an antibody or an antigen binding fragment of an antibody.

c. Claims 98 and 109-112 are indefinite for reciting "instructions describing the methods of using and uses for said antibody" in claim 98 because the exact meaning of the phrase is not clear. It is not clear what "uses" or "using" is contemplated. Is the use for labeling the antibody, purifying or producing the antibody, detection, treatment, diagnosis, etc?

d. Claim 108 recites the limitation "said toxin" in claim 106. There is insufficient antecedent basis for this limitation in the claim.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 99-100, 109-110 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been added and recite wherein the CDRs of said antibody or said anti-mesothelin antibody have 80% or 90% or greater sequence similarity to CDRs of SEQ ID NO:5. The response filed 2/11/02 states that support for the amendment can be found at page 17, line 18 through page 18, line 5 (see page 4 of response). Upon inspection of these pages it is found that support for "variants of the prototype sequence of SEQ ID NO:1 have at least 80% sequence similarity..." is found (see page 18, lines 2-4). It is not found that 80% or 90% or greater sequence similarity to CDRs of SEQ ID NO:5 is found. SEQ IS NO:5 is a protein sequence and SEQ ID NO:1 is a DNA sequence. Applicant is required to provide specific support for the limitations or remove them from the claims.

9. Claims 6-7, 13-14, 24-25, 99-100, 104-105, 109-110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-mesothelin antibody which comprises the VH and the VL of SEQ ID NO:5 and the VH and the VL which are encoded by SEQ ID NO:1, does not reasonably provide

enablement for an anti-mesothelin antibody that only has a VH or a VL of SEQ ID NO:5 or a VH or a VL encoded by SEQ ID NO:1, in other words the anti-mesothelin antibody needs to be encoded by SEQ ID NO:1 or has the VH and the VL of SEQ ID NO:5 or an antibody with 80% or 90% sequence similarity of the CDRs of SEQ ID NO:5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an antibody that comprises a specific VH or VL or is encoded by DNA for a VH or a VL wherein the antibody does not contain both VH and VL from SEQ ID NO:5 or DNA encoding the VH and the VL of SEQ ID NO:1 and an antibody with 80% or 90% sequence identity in the CDRs to the CDRs of SEQ ID NO:5.

The specification teaches an anti-mesothelin antibody which has a VH and VL of SEQ ID NO:5 encoded by SEQ ID NO:1.

The specification does not teach any a VH of SEQ ID NO:5 with just any VL or visa versa or an antibody which is 80% or 90% sequence identity in the CDRs of SEQ ID NO:5.

The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody have the required

binding function. In addition Colman (Research in Immunology 145:33-36, 1994) teach that a very conservative substitution may abolish binding while a non-conservative substitution may have very little effect on binding (see page 35, left column). Thus, it is unpredictable whether an antibody with 80% or 90% sequence similarity in the CDRs to a parent antibody would bind the antigen. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone

Therefore, in view of the lack of predictability in the art as evidenced by Rudikoff et al and Colman and in view of the lack of guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 3, 4, 10-12, 18, 20, 27-29, 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Chowdhury et al [a] (Molecular Immunology 34:9-20, 1/1997, IDS #10) as evidenced by Chowdhury et al [b] (J. Mol. Biol 281:917-928, 1998, IDS #10).

The claims recite an anti-mesothelin single chain antibody wherein the VL and VH are conjugated through a linker and binds with at least $3X10^{-8}$ M, an anti-mesothelin antibody produced by a method, and an immunoconjugate comprising a PE fragment bonded to an anti-mesothelin antibody. Claim 32 is interpreted to mean an ant-mesothelin antibody conjugated to the sequence of PE.

Chowdhury et al [a] teach single chain antibodies which bind to recombinant mesothelin and mesothelin expressed on cells (see page 18, left column). As evidenced by Chowdhury et al [b] the K1 antibody binds at 22 nM to recombinant mesothelin and binds to cells expressing mesothelin (see Table 1 and page 924, left column (Discussion)). Chowdhury et al [a] also teach an immunotoxin comprising an antibody and a PE toxin (see page 9, left column) and the amino acid sequence of K1.

With regard to claim 18, the method in which the antibody was produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

12. Claims 1, 3, 4, 9-10, 18, 20, 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Brinkmann et al (Int. J. Cancer 71:638-644, 5/97, IDS #10).

The claims recite an anti-mesothelin single chain antibody wherein the VL and VH are conjugated through a linker and binds with at least $3X10^{-8}$ M, an anti-mesothelin antibody produced by a method, and an immunoconjugate comprising a therapeutic label bonded to an anti-mesothelin antibody.

Brinkmann et al teach a single chain antibody with a linker linking the VL and VH (see Figure 1) and the Fab antibody binds recombinant mesothelin at 8nM (see page 643) and cells expressing mesothelin at 10nM. Brinkmann et al also teach the K1 antibody labeled with radioiodine (see page 640, left column). It would be inherent that the single chain which comprises a VL and VH identical to the Fab would bind with affinity of the Fab.

With regard to claim 18, the method in which the antibody was produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

13. Claims 1, 3-5, 9-12, 18-20, 22, 23, 27-32, 97, 102-103, 107 are rejected under 35 U.S.C. 102(a) as being anticipated by Pastan et al (WO 97/25068, published 7/17/97) as evidenced by Chowdhury et al ((J. Mol. Biol 281:917-928, 1998, IDS #10).

The claims recite an anti-mesothelin single chain antibody, dsFv, and recombinant immunotoxin, wherein the VL and VH are conjugated through a linker and binds with at least $3X10^{-8}$ M, an anti-mesothelin antibody produced by a method, an immunoconjugate comprising a therapeutic label bonded to an anti-mesothelin antibody or scFv and an immunoconjugate comprising an antibody and PE38 and compositions comprising a recombinant immunoconjugate. Claim 32 is interpreted to mean an ant-mesothelin antibody conjugated to the sequence of PE.

Pastan et al teach the K1 antibody which as evidenced by Chowdhury et al binds recombinant mesothelin and cells with the claimed affinity. Pastan et al teach dsFv, scFv, immunoconjugates of I125, PE38 (see page 29, lines 3-9) (as evidenced by the specification on page 30, lines 2-6, PE38 is composed of residues 253-364 and 381-613 of PE) that are recombinantly produced (see page 4, lines 28-35, page 8, lines 20-30, page 22-25, page 28-30).

With regard to claim 18, the method in which the antibody was produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a

different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

14. Claims 1, 9-12, 18, 20, 27-29, 32, 97, 107 are rejected under 35 U.S.C. 102(b) as being anticipated by Willingham et al (U.S. Patent 5,320,956, issued 6/94) as evidenced by Chowdhury et al (JMB 281:917-928, 1998, IDS # 10).

The claims have been described supra. Claim 32 is interpreted to mean an ant-mesothelin antibody conjugated to the sequence of PE.

Willingham et al teach the K1 antibody which as evidenced by Chowdhury et al binds recombinant mesothelin and cells at nM affinity (see table 1, page 924). Willingham et al also teach an immunotoxin comprising K1 and PE and the antibody is detectably labeled (see column 2, lines 41-43, see Table VI legend) and compositions comprising such in a pharmaceutically acceptable carrier (see column 2, lines 36-54).

With regard to claim 18, the method in which the antibody was produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1, 3-5, 9-12, 18-20, 22-23, 27-32, 97-98, 102-103, and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chowdhury et al [a] (Molecular Immunology 34:9-20, 1/1997, IDS #10) as evidenced by Chowdhury et al [b] (J. Mol. Biol 281:917-928, 1998, IDS #10).as applied to claims 1, 3, 4, 10-12, 18, 20, 27-29, 32 above, and further in view of Pastan et al (U.S. Patent 5,747,654, filed 6/93).

Claims 1, 3-5, 9-12, 18-20, 22-23, 27-32, 97, 102-103, and 107 have been described supra. Claim 98 recites a kit for detecting mesothelin comprising an antibody which has a dissociation constant of less than $3X10^{-8}$ M and instructions for use for the antibody. Claim 32 is interpreted to mean an anti-mesothelin antibody conjugated to the sequence of PE.

Chowdhury et al has been described supra. Chowdhury et al does not teach a dsFv, an antibody or single chain detectably labeled, fusion at the DNA level, PE38 immunotoxin, or compositions comprising a pharmaceutically acceptable carrier and an immunotoxin or a kit comprising an anti-mesothelin antibody. These deficiencies are made up for in the teachings of Pastan et al.

Pastan et al teach immunoconjugates comprising a scFv, dsFv with PE38 and the antibody binding fragments are conjugated recombinantly to PE 38 (see column 1, lines 41-43, column 2, lines 36-44, column 5, lines 11-14, column 7, lines 18-20, column 8, lines 65-66, column 9, lines 5-9, column 19-20).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Chowdhury et al with the method of Pastan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Chowdhury et al with the method of Pastan et al because Pastan et al teach the disulfide bond sites are in highly conserved framework regions and the sites can be found from sequence alignment (see column 19, lines 52-66) and the immunotoxins comprising PE38 are active in the form of a scFv or a dsFv (see column 26) and the disulfide stabilized antibodies allow the affinity of the antigen to be maintained (see column 1, lines 54-57). In addition, One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Chowdhury et al with the method of Pastan et al because Chowdhury et al teach the focus of the laboratory is on the development of immunotoxins and the antibodies can be useful for immunotoxins (see page 9).

With regard to claim 18, the method in which the antibody was produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

With regard to claim 98, although the claim recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. The printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new.* If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak (CA FC)217 USPQ 401 relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable

distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed articles. The antibodies of the claimed articles remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Thus the instructions for use included in a kit or article manufacture constitute an "intended use" for that kit or article of manufacture. Intended use does not impart patentable weight to a product. See MPEP 2111.03:

Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey, 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963)

In the instant case, the claim is drawn to a kit which comprises an anti-mesothelin antibody, and labeling instructions. The intended use which is recited on the label or package insert lacks a function relationship to the antibody because the insert

or label does not physically or chemically affect the chemical nature of the antibody within the article of manufacture, and furthermore, the antibody can still be used by the skilled artisan for other purposes. Therefore the antibodies which are comprised within the kit are unpatentable over the prior art antibodies, because they function equally effectively with or without the labeling, and accordingly *no functional relationship exists between the instructions for use and the antibodies.*

Thus the claims are addressed as being drawn to a kit comprising an antibody and the instructions on the medium bearing no patentable weight with regard to double patenting, 102, and 103 rejections.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 1, 3-5, 9-12, 18-20, 22-23, 27-32, 97, 102-103, 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brinkmann et al (Int. J. Cancer 71:638-644, 5/97, IDS #10) as applied to claims 1, 3, 4, 9-10, 18, 20, 27 above, and further in view of Pastan et al (U.S. Patent 5,747,654, filed 6/93).

The claims have been described supra. Claim 32 is interpreted to mean an anti-mesothelin antibody conjugated to the sequence of PE.

Brinkmann et al has been described supra. Brinkmann et al does not teach a dsFv, single chain detectably labeled, fusion at the DNA level, PE38 immunotoxin, or compositions comprising a pharmaceutically acceptable carrier and an immunotoxin or

a kit comprising an anti-mesothelin antibody. These deficiencies are made up for in the teachings of Pastan et al.

Pastan et al has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Brinkmann et al with the method of Pastan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Brinkmann et al with the method of Pastan et al because Pastan et al teach the disulfide bond sites are in highly conserved framework regions and the sites can be found from sequence alignment (see column 19, lines 52-66) and the immunotoxins comprising PE38 are active in the form of a scFv or a dsFv (see column 26) and the disulfide stabilized antibodies allow the affinity of the antigen to be maintained (see column 1, lines 54-57). In addition, One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Brinkmann et al with the method of Pastan et al because Brinkmann et al teach smaller disulfide stabilized Fv fragments can be used for diagnosis and therapeutic potential (see page 643-44)

With regard to claim 18, the method in which the antibody was produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself.

The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

With regard to claim 98, although the claim recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. The printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new.* If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak (CA FC)217 USPQ 401 relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed articles. The antibodies of the claimed articles remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Thus the instructions for use included in a kit or article manufacture constitute an "intended use" for that kit or article of manufacture. Intended use does not impart patentable weight to a product. See MPEP 2111.03:

Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference

as compared to the prior art. In re Casey, 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963)

In the instant case, the claim is drawn to a kit which comprises an anti-mesothelin antibody, and labeling instructions. The intended use which is recited on the label or package insert lacks a function relationship to the antibody because the insert or label does not physically or chemically affect the chemical nature of the antibody within the article of manufacture, and furthermore, the antibody can still be used by the skilled artisan for other purposes. Therefore the antibodies which are comprised within the kit are unpatentable over the prior art antibodies, because they function equally effectively with or without the labeling, and accordingly *no functional relationship exists between the instructions for use and the antibodies.*

Thus the claims are addressed as being drawn to a kit comprising an antibody and the instructions on the medium bearing no patentable weight with regard to double patenting, 102, and 103 rejections.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 1, 3-5, 9-12, 18-20, 22, 23, 27-32, 97, 98, 102-103, 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al (WO 97/25068, published 7/17/97) as evidenced by Chowdhury et al (JMB 281:917-928, 1998, IDS # 10).. Claim 32 is interpreted to mean an anti-mesothelin antibody conjugated to the sequence of PE.

Pastan et al has been described supra. Pastan et al does not teach a kit comprising an anti-mesothelin antibody.

With regard to claim 98, although the claim recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. The printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new.* If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak (CA

FC)217 USPQ 401 relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed articles. The antibodies of the claimed articles remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Thus the instructions for use included in a kit or article manufacture constitute an "intended use" for that kit or article of manufacture. Intended use does not impart patentable weight to a product. See MPEP 2111.03:

Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey, 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963)

In the instant case, the claim is drawn to a kit which comprises an anti-mesothelin antibody, and labeling instructions. The intended use which is recited on the label or package insert lacks a function relationship to the antibody because the insert or label does not physically or chemically affect the chemical nature of the antibody within the article of manufacture, and furthermore, the antibody can still be used by the skilled artisan for other purposes. Therefore the antibodies which are comprised within the kit are unpatentable over the prior art antibodies, because they function equally effectively with or without the labeling, and accordingly *no functional relationship exists between the instructions for use and the antibodies.*

Thus the claims are addressed as being drawn to a kit comprising an antibody and the instructions on the medium bearing no patentable weight with regard to double patenting, 102, and 103 rejections.

With regard to claim 18, the method in which the antibody was produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claims 1, 3-5, 9-12, 18-20, 22-23, 27-32, 97, 102-103, 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Willington et al (U.S. Patent 5,320,956) as evidenced by Chowdhury et al (JMB 281:917-928, 1998, IDS # 10) as applied to claims 1, 9-12, 18, 20, 27-29, 97, 107 above, and further in view of Pastan et al (U.S. Patent 5,747,654, filed 6/93).

The claims have been described supra. Claim 32 is interpreted to mean an anti-mesothelin antibody conjugated to the sequence of PE.

Willington et al has been described supra. Willingham et al does not teach a dsFv, scFv, single chain detectably labeled, fusion at the DNA level, PE38 immunotoxin, or compositions comprising a pharmaceutically acceptable carrier and an immunotoxin or a kit comprising an anti-mesothelin antibody. These deficiencies are made up for in the teachings of Pastan et al.

Pastan et al has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Willingham et al with the method of Pastan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Willingham et al with the method of Pastan et al because Pastan et al teach the disulfide bond sites are in highly conserved framework regions and the sites can be found from sequence alignment (see column 19, lines 52-66) and

the immunotoxins comprising PE38 are active in the form of a scFv or a dsFv (see column 26) and the disulfide stabilized antibodies allow the affinity of the antigen to be maintained (see column 1, lines 54-57). In addition, One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a scFV or a dsFv immunotoxin with the antibody as taught by Willingham et al with the method of Pastan et al because Willingham et al teach the conjugate of K1 and PE is active and K1 can be useful in treatment and immunotoxins of K1 can be used for therapy (see column 10).

With regard to claim 18, the method in which the antibody was produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

With regard to claim 98, although the claim recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. The printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new.* If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak (CA FC)217 USPQ 401 relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed articles. The antibodies of the claimed articles remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Thus the instructions for use included in a kit or article manufacture constitute an "intended use" for that kit or article of manufacture. Intended use does not impart patentable weight to a product. See MPEP 2111.03:

Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey, 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963)

In the instant case, the claim is drawn to a kit which comprises an anti-mesothelin antibody, and labeling instructions. The intended use which is recited on the label or package insert lacks a function relationship to the antibody because the insert or label does not physically or chemically affect the chemical nature of the antibody within the article of manufacture, and furthermore, the antibody can still be used by the skilled artisan for other purposes. Therefore the antibodies which are comprised within the kit are unpatentable over the prior art antibodies, because they function equally

effectively with or without the labeling, and accordingly *no functional relationship exists between the instructions for use and the antibodies.*

Thus the claims are addressed as being drawn to a kit comprising an antibody and the instructions on the medium bearing no patentable weight with regard to double patenting, 102, and 103 rejections.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

20. Claims 15-17 are in condition for allowance. Claims 2, 8, 21, 26, 101, and 106 are objected to as depending on a rejected claim.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

22. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the

Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879